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(54) Title: SUBSTITUTED BENZIMIDAZOLES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL USE

#### (57) Abstract

The novel compounds of formula (I), wherein R¹ and R², which are different, is each H, alkyl containing 1-4 carbon atoms or -C(O)-R6; one of R¹ or R² is always selected from the group -C(O)-R6; wherein R6 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms, R³ is the group -CH2OCOOR7, wherein R7 is alkyl containing 1-6 carbon atoms or benzyl; R⁴ and R⁵ are the same or different and selected from -CH3, -C2H5, (a), (b) and -CH2CH2OCH3, or R⁴ and R⁵ form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R⁴ and R⁵ is -CH2CH2CH2-, -CH2CH2- or -CH2- as well as pharmaceutical compositions containing such compounds as active ingredient, and the use of the compounds in medicine.

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Substituted benzimidazoles, process for their preparation and their pharmaceutical use

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#### DESCRIPTION

#### Field of the invention

- The object of the present invention is to provide novel compounds, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of peptic ulcer.
- The present invention also relates to the use of the compounds of the invention for inhibiting gastric acid secretion in mammals including man. In a more general sense, the compounds of the invention may be used for prevention and treatment of gastrointestinal inflammatory
- diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis, and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric
- antisecretory effect is desirable e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress
- ulceration. The compounds of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout.
- 35 The compounds may also be useful in the treatment of diseases related to bone metabolism disorders as well as

the treatment of glaucoma. The invention also relates to pharmaceutical compositions containing the compounds of the invention, as active ingredient. In a further aspect, the invention relates to processes for preparation of such new compounds and to the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

It is a specific primary object of the invention to 10 provide compounds with a high level of biovailability. The compounds of the invention will also exhibit good stability properties at neutral and acidic pH and a good potency in regard to inhibition of gastric acid secretion. The compounds of the invention will not block 15 the uptake of iodine into the thyroid gland. It has earlier been disclosed in several lectures from the company, where the inventors are working that thyroid toxicity depends on if the compounds are lipophilic or not. The inventors have now unexpectedly found that it is 20 not the lipophilicity that is the critical parameter. The claimed compounds, which include rather hydrophilic compounds, do not give any thyroid toxic effect and have at the same time high acid secretion inhibitory effect, good bioavailability and stability.

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#### Prior art and background of the invention

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents.

30 Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, BE 898 880, EP 124 495, EP 208 452, EP 221 041, EP 279 149, EP 176 308 and Derwent abstract 87-294449/42. Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 359 465.

#### The invention

The compounds of the formula I are effective as
inhibitors of gastric acid secretion in mammals including
man and in addition do not block the uptake of iodine
into the thyroid gland. It has also been found that the
compounds of the following formula I show high
bioavailability. Further, the compounds of the invention
exhibit a high chemical stability in solution at neutral
and acidic pH. The high chemical stability also at acidic
pH makes the compounds useful for non-enteric coated
peroral formulations.

15 The compounds of the invention are of the following formula I:

 $\begin{array}{c|c}
 & OR^5 \\
 & OR^4 & O \\
 & N \\
 & OR^4 & O \\
 & R^2
\end{array}$ 

wherein
25 R<sup>1</sup> and R<sup>2</sup>, which are different, is each H, alkyl
containing 1-4 carbon atoms or -C(O)-R<sup>6</sup>, one of R<sup>1</sup> or R<sup>2</sup>
is always selected from the group -C(O)-R<sup>6</sup>;

wherein

30 R<sup>6</sup> is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms

 $R^3$  is the group  $-CH_2OCOOR^7$ , wherein  $R^7$  is alkyl containing 1-6 carbon atoms or benzyl;

 ${ ext{R}}^4$  and  ${ ext{R}}^5$  are the same or different and selected from

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$$-CH_3$$
,  $-C_2H_5$ ,  $-CH_2 \longrightarrow$ ,  $-CH_2 \longrightarrow$  , and  $-CH_2CH_2OCH_3$ , or  $\mathbb{R}^4$ 

and R<sup>5</sup> form together with the adjacent oxygen atoms 5 attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by R4 and R<sup>5</sup> is -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>- or -CH<sub>2</sub>-.

It should be understood that the expressions "alkyl" and 10 "alkoxy" include straight and branched structures.

The structural isomers of the invention described in examples 1-6 may be used separately, or in equal or unequal mixtures.

15

The compounds of the invention of the formula I have an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers) or if they also contain one or more asymmetric carbon atoms, the compounds have two or 20 more diastereomeric forms, each existing in the two enantiomeric forms. Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. It should also be understood that all the diastereomeric 25 forms possible (pure enantiomers or racemic mixtures) are

Preferred groups of compounds of the formula I are:

30 1.

within the scope of the invention.

- Compounds, wherein  $R^3$  is  $-CH_2OCOOCH_2CH_3$ . Compounds, wherein  $R^1$  and  $R^2$  are selected from H, methyl or -C(0)-R<sup>6</sup>, wherein R<sup>6</sup> is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.
- Especially preferred benzimidazole structures are: 3.

COCH<sub>3</sub>

CH<sub>3</sub>

CH<sub>3</sub>

CH<sub>3</sub>

COCH<sub>3</sub>

N

CH<sub>3</sub>

COCH<sub>3</sub>

N

CH<sub>3</sub>

COCH<sub>3</sub>

N

CH<sub>3</sub>

10 N CCH<sub>3</sub> N CCCH<sub>2</sub>CCH<sub>3</sub>

5

15 N COCH<sub>2</sub>CH<sub>3</sub>

- 20 4. Especially preferred are compounds, wherein R<sup>4</sup> and R<sup>5</sup> are methyl.
  - 5. Especially preferred specific compounds of the invention are the compounds listed in the following tabulation

25  $\mathbb{R}^{5}$  $\mathbb{R}^3$  $\mathbb{R}^2$ R4  $R^{1}$ CH2OCOOCH2CH3 CH<sub>3</sub> CH<sub>3</sub> C(O)OCH3 CH3 сн<sub>2</sub>осоосн<sub>2</sub>сн<sub>3</sub> CH3 CH<sub>3</sub> C(O)OCH3 CH<sub>3</sub> 30 CH2OCOOCH2CH3 CH<sub>3</sub> CH<sub>3</sub> C(O)CH<sub>3</sub> CH<sub>3</sub> CH<sub>3</sub> CH2OCOOCH2CH3 CH3 CH3 C(O)CH3 35

It is believed that compounds of formula I are metabolized

into the corresponding compounds, wherein  $\mathbb{R}^3$  is H before exerting their effect.

#### Preparation

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The compounds of the invention may be prepared according to the following methods:

a) Reacting a compound of the formula II

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wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined under formula I, and Z, is either a metal cation such as Na+, K+, Li+ or Ag+ or a quaternary ammonium ion, such as tetrabutylammonium with alkyl chloromethyl carbonate or benzyl chloromethyl carbonate.

b) Reacting a compound of the formula II, wherein  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^5$  are as defined under formula I and Z is hydroxymethyl with a compound of the formula III,

25

$$x-c(0)-o-R^7$$
 III

wherein R<sup>7</sup> is as defined above and X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

The reactions according to a) and b) are suitably carried out under protective gas in absence of water. Suitable solvents are hydrocarbons such as toluene or benzene or halogenated hydrocarbons such as methylene chloride or

chloroform, or acetone, acetonitrile or dimethylformamide. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

c) Oxidizing a compound of the formula IV

5

$$\begin{array}{c|c}
 & OR^5 \\
 & OR^4 \\
 & N \\
 & OR^4 \\$$

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined under formula 15 I.

This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers, ketones.

The oxidation may also be carried out enzymatically by
using an oxidizing enzyme or microbiotically by using a
suitable microorganism. The structural isomers obtained,
may be separated by means of crystallization or
chromatography.

Racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active

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solvent. In the case of racemic diastereomeric mixtures these may be separated into diastereomeric pure enantiomers by means of chromatography or fractional crystallization.

5 The starting materials utilized in the methods a)-c) are in some cases unknown. These unknown starting materials may, be obtained according to processes known per se.

Alkyl chloromethyl carbonate and benzyl chloromethyl
carbonate may be obtained from the pertinent alcohol by
treatment with chloromethyl chloroformate in the presence
of pyridine.

Intermediates of the formula II, wherein Z is hydroxymethyl are obtained by reaction of the corresponding benzimidazole compound carrying H in the N-1 position with formaldehyde.

Starting materials of the formula III may be obtained by known methods, e.g. from an alcohol HOR<sup>7</sup> by treatment with phosgene or 1,1<sup>1</sup>-carbonyldiimidazole or p-nitrophenyl chloroformate.

For clinical use a compound of the invention is formulated into pharmaceutical formulations for oral, rectal, or other modes of administration. The pharmaceutical formulation contains a compound of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

35 In the preparation of pharmaceutical formulations containing a compound of the present invention in the form

of dosage units for oral administration a compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another 5 suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like, as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol 10 waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among 15 pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a 20 suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

25 Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine

30 capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopection, cellulose

35 derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain an active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

25

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbomethoxy-5-methyl-2-

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[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1<u>H</u>-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

- To a suspension of 0.45 g (1.1 mmol) of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]1H-benzimidazole and 0.25 g (1.8 mmol) of potassium carbonate anhydrous in 45 ml of dry acetonitrile, 0.21 g (1.5 mmol) of chloromethyl ethyl carbonate dissolved in 5 ml

  10 of acetonitrile was added. The reaction mixture was stirred at room temperature over night. The solvent was then removed in vacuo and the residue was diluted with methylene chloride and water. The organic solvent was dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave the crude product, which was chromatographed with silica gel and eluted with ethyl acetate to provide 0.94 g of a yellow oil which slowly crystallized. Recrystallization with ethanol yielded 0.25 g (44 %) of the title compounds as an isomeric mixture.
- 20 NMR data for the products are given below.

25

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Example 2. Preparation of 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-<u>1H</u>-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was obtained by crystallizing the isomeric mixture given in example 1 from ethanol.

NMR data are given below.

30 Example 3. Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

To a magnetically stirred suspension of potassium carbonate

anhydrous (0.48 g, 3.47 mmol) in 80 ml of dry acetonitrile 0.80 g (2.14 mmol) of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and 0.39 g (2.8 mmol) of chloromethyl ethyl carbonate dissolved in 10 ml of acetonitrile was added dropwise. Stirring was continued at room temperature for 20 hours. The solvent was removed in vacuo, the residue diluted with methylene chloride, the methylene chloride solution washed with water and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave the crude product which was chromatographed with silica gel and eluted with ethyl acetate to yield 0.63 g of an almost white crystalline solide. The product was recrystallized from ethyl acetate to give 0.50 g (49 %) of the title compounds as an isomeric mixture.

NMR data for the products are given below.

Example 4. Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-<u>1H</u>-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was isolated from the isomeric mixture given in example 3 by chromatography on a silica column with methylene chloride - acetonitrile (ratio 6:4) as eluent. The title compound was crystallized from ethanol.

NMR data are given below.

Example 5. Preparation of 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-<u>1H</u>-benzimidazole-1-ylmethyl ethyl carbonate.

The title compound was isolated from the isomeric mixture given in example 3 by chromatography on a silica column with methylene chloride-acetonitrile (ratio 6:4) as eluent. The title compound was crystallized from ethanol.

NMR data are given below.

Example 6 Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and 6-carbethoxy-2-[[(3,4-dimethoxy-2-

5 pyridinyl)methyl]sulfinyl]-1<u>H</u>-benzimidazole-1-ylmethyl ethyl carbonate, as an isomeric mixture.

To a suspension of 0.28 g (0.72 mmol) 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H benzimidazole and 0.16 g (1.2 mmol) anhydrous potassium carbonate in 20 ml of dry acetonitrile 0.16 g (1.2 mmol) chloromethyl ethyl carbonate dissolved in 2 ml dry acetonitrile was added. The mixture was stirred at ambient temperature over night. The solvent was evaporated off and the crude product was chromatographed on a silica column using ethyl acetate as eluent. Crystallizing from ethanol gave the title compounds as an isomeric mixture, (0.13 g, 37%).

NMR data for the products are given below.

#### 20 Table 1

	Ex.	Solvent	NMR data 8 ppm
	1	CDC13	1.20-1.30 (m, 3H), 2.70 (s,1.8H),
25		(300 MHz)	2.75 (s, 1.2H), 3.85-3.95 (m,9H),
			4.15-4.25 (m,2H), 4.85-5.05 (m,2H),
			6.40-6.55 (m,2H), 6.75 (d,1H), 7.45
			(s, 0.6H), 7.65 (s, 0.4 H), 8.10
			(d, 1H), 8.20 (s, 0.4 H), 8.40 (s,
30			0.6 H).
	2	CDC13	1.30 (t, 3H), 2.70 (s, 3H)
		(300 MHz)	3.90 (s,3H), 3.90 (s, 3H), 3.95 (s,
		•	3H), 4.25 (q, 2H), 4.95 (d, 1H), 5.05
35			(d, 1H), 6.50 (m, 2H), 6.75 (d, 1H),
		•	7.65 (s, 1H), 8.10 (d, 1H), 8.20 (s,

1H)

5	3	CDC1 <sub>3</sub> (300 MHz)	1.30 (t, 3H) 2.60-2.70 (m, 6H), 3.85-3.90 (m, 6H), 4.25 (q,2H), 4.85-5.05 (m, 2H), 6.75 (d,1H), 7.45 (s, 0.7 H), 7.60 (s, 0.3H), 8.05 (s, 0.3H), 8.10 (d, 1H), 8.20 (s, 0.7H)
10	4	CDC1 <sub>3</sub> (300 MHz)	1.30 (t, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.20 (q, 2H), 4.90 (d, 1H), 5.05 (d, 1H), 6.50 (m, 2H), 6.80 (d, 1H), 7.50 (s, 1H), 8.15 (d, 1H), 8.20 (s, 1H)
20	5	CDC1 <sub>3</sub> (300 MHz)	1.30 (t, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.25 (q, 2H), 4.90 (d, 1H), 5.05 (d, 1H), 6.55 (m, 2H), 6.80 (d, 1H), 7.60 (s, 1H), 8.05 (s, 1
25	6	CDC1 <sub>3</sub> (300 MHz)	H), 8.15 (d, 1H)  1.30 (m, 3H), 1.45 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.25 (m, 2H), 4.45 (m, 2H), 5.00 (m, 2H), 6.55 (m, 2H), 6.80 (d, 1H), 7.70 (d, 0.55H), 7.80 (d, 0.45H), 8.10 (m, 2H), 8.35 (s, 0,45H), 8.50 (d, 0.55H).

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#### Preparation of intermediates

#### Example I 1

5 Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-lH-benzimidazole

5-carbomethoxy-6-methyl-2-mercapto-1<u>H</u>-benzimidazole (0.67 g, 0.003 mol) and NaOH (0.12 g, 0.003 mol) in H<sub>2</sub>O (0.6 ml)

10 were dissolved in CH<sub>3</sub>OH (15 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride, (≈0.0036 mol) as a crude material in CH<sub>3</sub>OH (10 ml) and NaOH (0.144 g, 0.0036 mol) in H<sub>2</sub>O (0.72 ml) were added. The mixture was heated to reflux and the reflux was continued for 1 hour. CH<sub>3</sub>OH was evaporated off and the crude material was purified by chromatography on a silica column using CH<sub>2</sub>Cl<sub>2</sub>-CH<sub>3</sub>OH (98-2) as eluent, giving (1.03 g, 92%) of the pure title compound.

NMR data are given below.

20

#### Example I 2

Preparation of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

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5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1<u>H</u>-benzimidazole (1.03 g, 0.00276 mol) was dissolved in  $CH_2Cl_2$  (30 ml). NaHCO<sub>3</sub> (0.46 g, 0.0055 mol) in  $H_2O$  (10 ml) was added and the mixture was cooled to  $+2^OC$ . m-chloroperbenzoic acid 69.5% (0.62 g, 0.0025 mol) dissolved in  $CH_2Cl_2$  (5 ml) was added dropwise under stirring. Stirring was continued at  $+2^OC$  for 15 min. After separation the organic layer was extracted with an aqueous 0.2 M NaOH solution (3x15 ml, 0.009 mol). After separation the aqueous solutions were combined and neutralized with methyl formate (0.56 ml, 0.009 mol) in the

presence of  $CH_2Cl_2$  (25 ml). After separation the organic layer was dried over  $Na_2SO_4$  and evaporated under reduced pressure. The residue was crystallized from  $CH_3CN$  (10 ml) giving the title compound (0.68 g, 70 %).

5

NMR data are given below.

#### Example I 3

# Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-acetyl-6-methyl-2-mercapto-1<u>H</u>-benzimidazole (4.2 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in H<sub>2</sub>O (1 ml) were dissolved in 60 ml ethanol. 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (\*17 mmol) as a crude material was added and the mixture was heated to boiling. NaOH (0.7 g, 17 mmol) in H<sub>2</sub>O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure. Crystallizing from acetonitrile gave the title compound, (3.75 g, 62%).

25 NMR data are given below.

#### Example I 4

## Preparation of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-30 pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.75 g, 10 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (70 ml). NaHCO<sub>3</sub> (1.76 g, 21 mmol) in H<sub>2</sub>O (25 ml) was added and the mixture was cooled to ≈+3<sup>O</sup>C. m-Chloroperbenzoic acid 69.5% (2.43 g, 9.8 mmol) dissolved

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in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added dropwise under stirring.

Stirring was continued for 10 min. The phases were separated and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was crystallized from 5 CH<sub>2</sub>CN giving the title compound (2.25 g, 60%).

NMR data are given below.

#### Example I 5

10

Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-lH-benzimidazole

5-carbethoxy-2-mercapto-1H-benzimidazole (2.0 g, 9 mmol) and
15 NaOH (0.36 g, 9 mmol) in H<sub>2</sub>O (1 ml) were dissolved in
ethanol (30 ml). 3,4-dimethoxy-2-chloromethylpyridine
hydrochloride (≈6.6 mmol) as a crude material were added and
the mixture was heated to boiling. NaOH (0.26 g, 6.6 mmol)
in H<sub>2</sub>O (1 ml) was added and the reflux was continued for 6
20 hours. The solvent was evaporated off and the residue was
diluted with methylene chloride and water. The organic phase
was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed under reduced
pressure. Crystallizing from CH<sub>3</sub>CN gave the desired product
(1.75 g, 71 %).

25

NMR data are given below.

#### Example I 6

30 Preparation of 5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1<u>H</u>-benzimidazole

5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]1H-benzimidazole (95.2% pure) (1.4 g, 0.0036 mol) was
35 dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 ml). NaHCO<sub>3</sub> (0.6 g, 0.0072 mol in H<sub>2</sub>O (10 ml) was added and the mixture was cooled to +2<sup>O</sup>C.

m-Chloroperbenzoic acid 69.5 % (0.87 g, 0.0035 mol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added dropwise under stirring. Stirring was continued at +2°C for 10 min. The phases were separated and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The residue was crystallized from CH<sub>3</sub>CN (15 ml) giving the title compound (0.76 g, 54 %).

NMR data are given below.

10

#### Table 2

	Ex	Solvent	NMR data 6 ppm
15	I 1	CDC1 <sub>3</sub> (300 MHz)	2.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H),
			4.40 (s, 2H), 6.90 (d, 1H), 7.35 (s, 1H), 8.20 (s, 1H),
20			8.25 (d,1H).
	I 2	CDC1 <sub>3</sub> (500 MHz)	2.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H),
25			6.8 (d, 1H), 7.30 (b, 1H), 8.20 (d, 1H), 8.35 (b, 1H).
	I 3	CDC1 <sub>3</sub> (300 MHz)	2.60 (s, 3H), 2.65 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.35 (s, 2H) 6.85 (d, 1H), 7.25 (s,0.6H), 7.40
30			(s, 0.4H), 7.85 (s, 0.4H), 8.05 (s, 0.6H), 8.30 (m, 1H)
35	I 4	CDC1 <sub>3</sub> (300 MHz)	2.60 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.80 (d, 1H), 7.30 (b, 1H), 8.15 (d, 1H), 8.20 (b, 1H)

I 5	CDCl <sub>3</sub> (300 MHz)	1.40 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.40 (m, 4H), 6.90 (dd, 1H), 7.45 (d, 0.4H), 7.60 (d, 0.6H), 7.90 (m, 1H), 8.20 (s, 0.6H), 8.25 (m, 1H), 8.25 (s, 0.4H)
10 I 6	CDCl <sub>3</sub> (300 MHz)	1.45 (t, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.40 (q, 2H), 4.65 (d, 1H), 4.40 (d, 1H), 6.80 (d, 1H), 7.50 7.80 (b, 1H)
15		8.05 (d, 1H), 8.20 (d, 1H), 8.25, 8.55 (b, 1H)

The best mode of carrying out the invention known at present is to use the compound mixture according to Example 3 and the compound according to Example 4.

mixture

Isomeric

NMR

37

CH<sub>3</sub>

CH<sub>3</sub>

CH20COOC2H5

с(о)осн<sub>2</sub>сн<sub>3</sub> н н с(о)осн<sub>2</sub>сн<sub>3</sub>

9

		_			
.le.	Ident. data	NMR	NMR	NMR	NMR
lowing tab	Yield \$	44		49	
the fol:	R <sub>5</sub>	CH <sub>3</sub> 44	СН3	СН3	сн3
re given in	*≃	CH <sub>3</sub>	GH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>
e formula I a	R <sup>3</sup>	сн <sup>2</sup> осоос <sup>2</sup> н <sup>2</sup>	cH <sub>2</sub> ocooc <sub>2</sub> H <sub>5</sub>	сн <sub>2</sub> осоос <sub>2</sub> н <sub>5</sub>	cH <sub>2</sub> ocooc <sub>2</sub> H <sub>5</sub>
Examples of compounds included in the formula I are given in the following table.	<b>R</b> 2	сн <sub>3</sub> сі	c(o)och <sup>3</sup> c	сн <sub>з</sub> с с(о)сн <sub>з</sub>	CH <sub>3</sub> CI
of compounds i	R	с(о)осн <sub>3</sub> сн <sub>3</sub>	сн3	с(о)сн <sub>3</sub> сн <sub>3</sub>	с(о)сн <sup>3</sup>
Examples	Example		2	m	₹*

Isomeric

Remarks mixture

20

mixture

Isolated

isomer

Isolated

MMR

 $cH_3$ 

CH<sub>3</sub>

 $c_{\rm H_2}$ 

C(0)CH3

CH<sub>3</sub>

Ŋ

isomer

Isomeric

Isolated

**isomer** 

able

#### Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

5 1.0 g A compound according to Example 4 30.0 g Sugar, powder 0.6 g Saccharine 5.0 g Glycerol 1.0 g 10 Tween 0.05 g Flavouring agent 5.0 g Ethanol 96% 100 ml Distilled water q.s. to a final volume of

15 A solution of the compound mixture according to Example in ethanol and Tween was prepared. Sugar and saccharine were dissolved in 60 g of warm water. After cooling the solution of the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

#### <u>Tablets</u>

25 A tablet containing 50 mg of active compound was prepared from the following ingredients:

1	compound mixture according to		
	Example 3	500	g
	Lactose	700	g
	Methyl cellulose	6	g
	Polyvinylpyrrolidone cross-linked	50	g
	Magnesium stearate	15	g
	Sodium carbonate	6	g
	Distilled water	q.	s.
	1	Example 3 Lactose Methyl cellulose Polyvinylpyrrolidone cross-linked Magnesium stearate Sodium carbonate	Example 3 500 Lactose 700 Methyl cellulose 6 Polyvinylpyrrolidone cross-linked 50 Magnesium stearate 15 Sodium carbonate 6

II	Hydroxypropyl methylcellulose	36 g
	Polyethylene glyco	19 g
	Colour Titanium dioxide	4 g
	Purified water	313 g

I Compound mixture according to Example 3, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of hydroxypropyl methylcellulose and polyethylene glycol in purified water was prepared. After dispersion of titanium dioxide the solution was sprayed onto the tablets I in an Accela Cota<sup>R</sup>, Manesty coating equipment. A final tablet weight of 125 mg was obtained.

#### Capsules

25 Capsules containing 30 mg of active compound were prepared from the following ingredients:

	A compound according to Example 4	300	g
	Lactose	700	g
30	Microcrystalline cellulose	40	g
	Hydroxypropyl cellulose low-substituted	62	g
	Purified water	q.	s.

The active compound mixture was mixed with the dry

ingredients and granulated with a solution of disodium

hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

5 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 600 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below: Coating solution:

10

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	<b>4</b> g
Acetone	600 g
Pthanol	200 g

15

The final coated pellets were filled into capsules.

#### Suppositories

20 Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

	Compound mi	xture	according	to	Example	4	4 (	3
25	Witepsol H-	-15					180 9	g

The active compound mixture was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

### Biological Effects

#### Biovailability

5

Bioavailability, is assessed by calculating the quotient between the areas under plasma concentration (AUC) curve of a compound of the formula I wherein R<sup>3</sup> is hydrogen (herein defined as compound A), following 1) intraduodenal (id) or oral (po) administration of the corresponding compound according to the invention and 2) intravenous (iv) administration of compound A, from the rat and the dog. Low, therapeutically relevant doses, were used. Data are provided in Table 4.

15

#### Potency for inhibition of acid secretion

The potency for inhibition of acid secretion is measured in the female rat orally and in the dog both 20 intraduodenally and orally.

Potency data are provided in Table 4.

#### Effects on the uptake of iodine into the thyroid gland.

25

The effect of a compound within the invention of the formula I on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of <sup>125</sup>I in the thyroid gland of the corresponding compound of the formula I, wherein R<sup>3</sup> is hydrogen, that is a metabolized compound of the formula I.

#### Biological Tests

35 Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen), for collection of gastric secretions. A fourteen days recovery period after surgery is allowed before testing is commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed 10 through the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion is stimulated with infusion during 2.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions are collected in 30-min 15 fractions. Test substances or vehicle are given orally 120 min before starting the stimulation, in a volume of 5 ml/kg. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume and concentration. Further 20 calculations are based on group mean responses from 4-7 rats. Percentage inhibition is calculated from absolute rates of acid output. ED<sub>50</sub>- values are obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar 25 slope for all dose-response curves. The results are based on gastric acid secretion during the third hour after drug/vehicle administration.

Bioavailability in the Male Rat.

30

Male adult rats of the Sprague-Dawley strain were used.

One day, prior to the experiments, all rats were prepared
by cannulation of the left carotid artery under
anaesthesia. The rats used for the intravenous
experiments, were also cannulated in the jugular vein.

(Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck.
5 The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substances. The same dose (4 μmol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

- 10 Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until analysis of the test compound.
- The area under the blood concentration vs time curve, AUC, for the compound A, determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic
- 20 bioavailability (F%) of the compound A following intraduodenal administration of compounds of the invention of formula I was calculated as

Inhibition of Gastric Acid Secretion and Bioavailability 30 in the Conscious Dog

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhain-pouch for the collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine 5 dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given orally, id or iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg 10 body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenhain-pouch dog.

15 The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED50values were obtained by graphical interpolation on log dose - response curves, or estimated from single-dose 25 experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

Blood samples for the analysis of test compound 30 concentration in plasma were taken at intervals up to 3 h after dosing. Plasma was separated and frozen within 30 min after collection and later analyzed. AUC (area under the plasma concentration - time curve) from time zero to 3 h after dose for compound A, was calculated by the linear 35 trapezoidal rule. The systemic bioavailability (F%) of the compound A after oral or id administration of compounds of the invention was calculated as described above in the rat model.

# 5 Refrect on the accumulation of 125 I in the thyroid gland

The accumulation of <sup>125</sup>I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950; 47:77-81) was followed.

Test substances, suspended in 0.5% buffered (pH 9) methocel, were administerd by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, 125I (300kBq/kg, 3ml/kg) 15 was administered by intraperitoneal injection. Four hours after 125 I-administration, the animals were killed by CO2-asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma 20 counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula 100 (1-T/P), where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered methocel), respectively. The statistical 25 significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). P<0.05 was accepted as significant.

#### Chemical Stability

30

The chemical stability of the compounds of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 5 show the half life (t 1/2) at pH 7, that is the time period after which half the amount of the

original compound remains unchanged, and <sup>t</sup>10% at pH 2, that is the time period after which 10% of the original compound has decomposed.

# 5 Results of biological and stability tests

Table 4 and 5 give a summary of the test data available for the compounds of the invention.

Table 4, Biological Test Data

					30				
Per cent inhibition of 400 µmol/kg <sub>1</sub> 2g the uptake of	in the thyroid gland		0	0	<b>L-</b>	L-	-7	9	
Blovailability F%	Rat	id adm	106		66				
aila  F%		1d adm			(q99				_
Biov	Dog	oral adm	51 <sup>b)</sup>		51 <sup>b)</sup> 66 <sup>b)</sup>	35 <sup>b)</sup>	(q05		_
Inhibition of acid secretion, id administration	Dog, KD <sub>50</sub> umol/kg		1.3a)		1.3a) 0.8b)		-		
on of acid on, oral tration	ol/Kg	Rat			6.0				-
Inhibition of acservation, ora- administration	EUSO MOLIKG	Dog	1.0 <sup>b)</sup>		1.5 <sup>b)</sup>	2.2 <sup>b)</sup>	1.5 <sup>b)</sup>		
Test compound Inhibition of acid Example no. secretion, oral administration			н	2	ю	4	Ŋ	v	

a) gastric fistula dog b) Heidenhain pouch dog

# Table 5, Stability Data

Test compound Example No.	Chemical stability at pH 7 pH 2 t 1/2 (h) t 10% (h)
1	87 9.5
2	50 6.5
3	51 7.5
4	82 13
5	60 7
e	. 63 13

10

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#### CLAIMS:

1. Compounds of the formula I

OR5
OR4
ON
R1
R2

wherein

 $R^1$  and  $R^2$ , which are different, is each H, alkyl containing 1-4 carbon atoms or  $-C(0)-R^6$ ; one of  $R^1$  or  $R^2$  is always selected from the group  $-C(0)-R^6$ ;

wherein

R<sup>6</sup> is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms,

20 R<sup>3</sup> is the group -CH<sub>2</sub>OCOOR<sup>7</sup>, wherein R<sup>7</sup> is alkyl containing 1-6 carbon atoms or benzyl;

 $R^4$  and  $R^5$  are the same or different and selected from  $-CH_3$ ,

25 
$$-c_2H_5$$
,  $-cH_2$ ,  $-cH_2$  and  $-cH_2CH_2OCH_3$ , or  $R^4$  and  $R^5$ 

form together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring a ring, wherein the part constituted by  $R^4$  and  $R^5$  is  $-CH_2CH_2$  -  $-CH_2CH_2$ 

- 30 CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>- or -CH<sub>2</sub>-.
- Compounds according to formula I of claim 1, namely a mixture of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl
   ethyl carbonate and 6-carbomethoxy-5-methyl-2-[[(3,4-

dimethoxy-2-pyridinyl)methyl]sulfinyl]-H-benzimidazole-1-ylmethyl ethyl carbonate.

- 3. Compounds according to formula I of claim 1, namely
  5 mixture of 5-acetyl-6-methyl-2-[[(3,4-dimethoxy-2pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl
  ethyl carbonate and 6-acetyl-5-methyl-2-[[(3,4-dimethoxy2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl
  ethyl carbonate.
- 4. A compound according to claim 1, namely 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]- $1\underline{H}$ -benzimidazole-1-ylmethyl ethyl carbonate.
- 15 5. A compound according to claim 1, namely 6-carbomethoxy-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.
- 6. A compound according to claim 1, namely 5-acetyl-6-20 methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1Hbenzimidazole-1-ylmethyl ethyl carbonate.
- 7. A compound according to claim 1, namely 6-acetyl-5-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sufinyl]-1<u>H</u>-benzimidazole-1-ylmethyl ethyl carbonate.
  - 8. A compound according to claim 1, wherein  $\mathbb{R}^3$  is the group  $\mathrm{CH_2OCOOCH_2CH_3}$ .
- 30 9. A compound according to claim 1, wherein  $R^1$  and  $R^2$  is each H, methyl or  $-C(0)R^6$ , wherein  $R^6$  is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.
- 10. A pharmaceutical composition containing as active ingredient a compound according to claim 1.

- 11. A compound as defined in claim 1 for use in therapy.
- 12. A compound as defined in claim 1 for use in inhibiting gastric acid secretion in mammals including man.
- 13. A compound as defined in claim 1 for use in the treatment of gastrointestinal inflammatory deseases in mammals including man.
- 10 14. A method for inhibiting gastric acid secretion by administering to mammals including man a compound as defined in claim 1.
- 15. A method for the treatment of gastrointestinal infammatory diseases in mammals including man by administering a compound as defined in claim 1.
- 16. Use of a compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid20 secretion in mammals including man.
- 17. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including 25 man.
  - 18. A process for the preparation of a compound of the formula I according to claim 1, by
  - a) reacting a compound of the formula II

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35

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined under formula I and Z is either a metal cation such as Na+, K+, Li+ or Ag+ or a quaternary ammonium ion, such as tetrabutylammonium with alkyl chloromethyl carbonate or benzyl chloromethyl carbonate or;

b) reacting a compound of the formula II, wherein  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^5$  are as defined under formula I and Z is hydroxymethyl with a compound of the formula III

10

$$x-c(0)-0-R^7$$

wherein R<sup>7</sup> is as defined above and X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group in the presence of a suitable base such as triethylamine or;

c) oxidizing a compound of the formula IV

20

25

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined under formula I.

#### INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00415

I. CLASSIFICATION	SIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) <sup>6</sup>		
	ational Patent Classification (IPC) or to both 401/12, A 61 K 31/415, 3		
II. FIELDS SEARC		.7	
		entation Searched 7	
Classification System		Classification Symbols	
IPC5	C 07 D		
		er than Minimum Documentation its are included in Fields Searched <sup>8</sup>	
SE,DK,FI,NO	classes as above		
III. DOCUMENTS C	ONSIDERED TO BE RELEVANTS		
Category * Cita	tion of Document, <sup>11</sup> with indication, where ap	propriate, of the relevant passages 12	Relevant to Claim No. <sup>13</sup>
6	, 0221041 (AKTIEBOLAGET HA May 1987, ee the whole document 	SSLE)	1-13,16- 18
2	, 0176308 (THE UPJOHN COMF April 1986, ee the whole document 	PANY)	1-13,16- 18
•			
"A" document deficansidered to "E" earlier document which is cited citation or oth	ies of cited documents: 10 ning the general state of the art which is not be of particular relevance ent but published on or after the internationa ch may throw doubts on priority claim(e) or to establish the publication date of another er special reason (as specified) rring to an oral disclosure, use, exhibition or	"Y" Coscinent of particular relevance Control of Costinent of particular relevance Control of Contr	e, the claimed invention annot be considered to
other means	ished prior to the international filing date bu	in the art.	
	ished prior to the international filing date bu priority date claimed	"&" document member of the same (	Patent lamily
IV. CERTIFICATION  Date of the Actual Con	mpletion of the International Search	Date of Mailing of this international Se	arch Report
5th September		1991 -09-	19
International Searchir	g Authority	Signature of Authorized Officer	
SWED	ISH PATENT OFFICE	Göran Karlsson	··

International Application No. PCT/SE 91/00415

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET	
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V. X OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE	
This international search report has not been established in respect of certain claims under Article 17(2) (a) for t  1. X Claim numbers 14-15 because they relate to subject matter not required to be searched by this Authorit	the following reasons:
A method for treatment of the human or animal body by therapy, see rule 39.1.	,
Claim numbers herause they relate to parts of the intermediant set in the second second set in the second seco	
2. Claim numbers because they relate to parts of the international application that do not comply wit requirements to such an extent that no meaningful international search can be carried out, specifically:	th the prescribed
	_
-	
3. Claim numbers because they are dependent claims and are not drafted in accordance with the sec	cond and third sen-
VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2	
This international Searching Authority found multiple inventions in this international application as follows:	
s totiows:	
As all required additional search fees were timely paid by the applicant, this international search report or claims of the international application.	overs all searchable
<ol> <li>As only some of the required additional search fees were timely paid by the applicant, this international sonly those claims of the international application for which fees were paid, specifically claims:</li> </ol>	search report covers
3. No required additional search fees were timely paid by the applicant. Consequently, this international sear ed to the invention first mentioned in the the claims, it is covered by claim numbers:	rch report is restrict-
- 55 to the invention instringment in the the claims. It is covered by claim numbers:	
4. As all searchable claims could be searched without effort justifying an additional fee, the International Section 2.	arching Authority
Remark on Protest	ļ
The additional search fees were accompanied by applicant's protest.	
No protest accompanied the payment of additional seach fees.	

Form PCT/ISA/210 (supplemental sheet (2)) (January 1985)

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00415

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-07-31

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Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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